# Statistical Analysis Plan for "Estimation of vaginal ring efficacy using HOPE and ASPIRE clinical trials"

January 7, 2020

## 1 Objectives

The ASPIRE clinical trial (MTN-020) evaluated the HIV prevention efficacy of a vaginal ring containing the ARV drug dapivirine relative to a placebo ring. The trial showed that the ring had 27% effectiveness (should we also mention the 37% efficacy once two sites excluded?). The open-label extension study HOPE (MNT-025) followed women from ASPIRE who had not yet become HIV positive and who volunteered to participate. All of these women were provided access to the vaginal ring. In this work, we seek to evaluate the open-label efficacy of the vaginal ring versus placebo for the population enrolled in HOPE. Estimating this quantity is challenging due to an absence of placebo recipients enrolled in HOPE. Our analysis strategy will involve leveraging information from ASPIRE to predict the open-label HIV prevention efficacy of the ring that would have been estimable from HOPE trial data had participants been randomized to either an active or placebo arm in that trial.[1]

The subgroup of individuals who are HIV-uninfected at the end of ASPIRE may differ depending on the intervention that the individual received in ASPIRE. For example, this subgroup may be more enriched for adherent individuals in the active arm than it is in the placebo arm. As a consequence, we believe that the open-label efficacy that we consider will have the most natural interpretation when the analysis is stratified by randomization assignment in the ASPIRE trial.

### 1.1 Primary Objectives

1. Evaluate the open-label efficacy of the vaginal ring versus placebo in the HOPE trial within subgroups defined by randomization assignment in the ASPIRE trial.

### 1.2 Secondary Objectives

2. Evaluate Objective 1 within subgroups defined by age.

[1] We need to put down a more formal definition of what we mean by "open-label efficacy" – in this counterfactual scenario, would the placebos be aware that they're receiving placebo? I'd think not

3. Estimate the survival curve for time until HIV infection for the HOPE trial study population during the HOPE trial.

# 2 Notation

For each individual in our data set, we suppose that there is a true underlying HIV infection time $T$ (We should probably define what $T = 0$ is) (Time of enrollment in aspire) and a right-censoring time $C$. We suppose that we observe $n$ independent copies of a tuple $X$ containing the following random variables, where $X$ is drawn from some distribution $P_0$:

- $L(0)$: baseline covariates in ASPIRE;
- $A(0)$: indicator of randomization to the active arm in ASPIRE;
- $U$: time in months between when the participant enrolled in the study and when ASPIRE concluded follow-up;[2]
- $V$: time in months at which the participant enrolled in HOPE, relative to the time at which the participant enrolled in ASPIRE;
- $H(V)$: an indicator of an individual's enrollment in HOPE (necessarily 0 if HIV infected before Month $V$);
- $L(V)$: covariates at the beginning of HOPE (by convention, $(0, \ldots, 0)$ if $H(V) = 0$);[3]
- $A(V)$: indicator of randomization to the active arm in HOPE (1 for all individuals enrolled in HOPE, and, by convention, 0 for all individuals with $H(V) = 0$);
- $\tilde{T} := \min\{T, C\}$: length of infection-free follow-up; and
- $\Delta = I\{T \leq C\}$: indicator of having observed $T$.

For $t \in [0, V + 12]$ (Reading the protocol, it appears that they follow patients for 13 months, although I am not sure 12 is not the correct thing to write here.), we also define $Y(t) := I\{T \leq t\}$, where $Y(t)$ denotes an indicator of being HIV infected at Month $t$. Note that $Y(t)$ is known whenever $\Delta = 1$ or $\tilde{T} \geq t$. For much of our discussion, it will prove convenient to ignore the censored nature of $Y(t)$, and instead assume that $Y(t)$ is observed. Under the assumption that $C \perp\!\!\!\perp T|L(0)$, we will later show that we can properly account for the fact that $Y(t)$ is in fact missing for some individuals.

We also assume that there exist counterfactuals corresponding to the values these variables would take under interventions on $A(0)$, $H(V)$, and $A(V)$. In particular, we let:

- $Y_{a(0)}(t)$, $t \in (0, U]$: the indicator of being HIV infected at Month t in a counterfactual world where the individual was randomized to the $a(0)$ arm in ASPIRE;

[2] ASPIRE was an event-driven trial that terminated at the later of (i) the time at which the target number of events had been reached, and (ii) the time at which the final-enrolled participant had accrued 12 months of follow-up.

[3] $L(V)$ contains the same covariates as those that were measured at the beginning of ASPIRE.

- $H_{a(0)}(V)$: an indicator of an individual's decision to enroll in HOPE in a counterfactual world where the individual was randomized to the $a(0)$ arm in ASPIRE (necessarily 0 if $Y_{a(0)}(V) = 1$);
- $L_{a(0),1}(V)$: covariates at the beginning of HOPE in a counterfactual world where the individual was randomized to the $a(0)$ arm in ASPIRE and enrolled in HOPE (by convention, $(0, \ldots, 0)$ if $Y_{a(0)}(V) = 1$);
- $Y_{a(0),1,a(V)}(t)$, $t \in (V, V + 12]$: the indicator of being HIV infected at Month t in a counterfactual world where the individual was randomized to the $a(0)$ arm in ASPIRE, enrolled in HOPE, and was assigned to the $a(V)$ arm in HOPE.

We will use $\mathbb{E}$ to denote expectations over the full data distribution of the random variable

$$X^F := \Big( U, V, L(0), \Big(Y_{a(0)}(t) : t \in (0, U], a(0) \in \{0, 1\}\Big), H_0(V), H_1(V), \\ L_{a(0),1}(V), \Big(Y_{a(0),1,a(V)}(t) : t \in (V, V + 12], a(0) \in \{0, 1\}, a(V) \in \{0, 1\}\Big)\Big).$$

# 3 Objective 1: open-label efficacy of the vaginal ring vs. placebo in the HOPE trial

We repeat the estimation strategy described in this section for $a(0) = 0$ and $a(0) = 1$.

## 3.1 Target of estimation

Our objective is to contrast the following two quantities:

$$\psi^F_{a(0),0} := \mathbb{E}[Y_{a(0),1,0}(V + 12)|H_{a(0)}(V) = 1], \\ \psi^F_{a(0),1} := \mathbb{E}[Y_{a(0),1,1}(V + 12)|H_{a(0)}(V) = 1]. \tag{1}$$

We will report estimates of the reduction in HIV incidence in the active arm relative to the placebo arm (i) on an additive scale, yielding the contrast $\psi^F_{a(0),0} - \psi^F_{a(0),1}$, and (ii) on a multiplicative scale, yielding the contrast $1 - \psi^F_{a(0),1}/\psi^F_{a(0),0}$.

## 3.2 Identifying assumptions

we'll fill in the ♣'s in this section later

♣ usual longitudinal causal assumptions ♣

Before listing our sequential randomization assumptions, we note that, by the design of the ASPIRE trial,

$$A(0) \perp\!\!\!\perp X^F. \tag{2}$$

♣

Let $\nu$ denote the conditional distribution of $L_{a(0),1}(V)$ given $H_{a(0)}(V)$. We make the following time-constancy assumption on the relative risk of HIV infection on the active arm versus on the placebo arm:[4]

$$\frac{\mathbb{E}[Y_1(12)|L(0)=\ell]}{\mathbb{E}[Y_0(12)|L(0)=\ell]} = \frac{\mathbb{E}[Y_{a(0),1,1}(V+12)|Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]}{\mathbb{E}[Y_{a(0),1,0}(V+12)|Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]} \text{ for a.s.-}\nu. \quad (3)$$

Notably, the expectations on the right-hand side condition on being HIV uninfected at Month $V$, namely on $Y_{a(0)}(V)=0$, rather than on choosing to enroll in HOPE at Month $V$, namely on $H_{a(0)}(V)=1$. Contrast this with the definition of the marginal means in (1), which do condition on enrollment into the HOPE study. We decided to condition on $H_{a(0)}(V)=1$ in the definition of these marginal means so that the efficacy parameter that we study for our primary analysis has the interpretation of being the efficacy that would have been observed in the population considered in HOPE had the assigned intervention been randomized between an active ring and a placebo ring in that study. We decided not to condition on $H_{a(0)}(V)=1$ in the right-hand side above because the subset of those non-HIV infected individuals at Month $V$ in with Month $V$ covariate value $\ell$ who chose to enroll in HOPE may not be representative of all such individuals and, consequently, may have a different multiplicative efficacy for the ring intervention.[5]

As we will see, (3) will make it possible to bridge results from the ASPIRE trial to learn about what the HIV incidence in the placebo arm would have been in the HOPE trial in the counterfactual world where a placebo arm had been included in this trial.

We note that (3) may be more plausible when $a(0)=0$, since in this case the initiation of the HOPE study represents the first time at which the individual was given access to the active intervention. When $a(0)=1$, one might conjecture that those individuals who are not HIV infected at Month $U$ may have a higher individual-level ring efficacy than those individuals who were on the active arm and became HIV infected before Month $U$, that is, that $Y_0(12)-Y_1(12)$ is often larger for the former group.[6] As a consequence, (3) may not be plausible. Nonetheless, the following bound may be plausible when $a(0)=1$:

$$\frac{\mathbb{E}[Y_1(12)|L(0)=\ell]}{\mathbb{E}[Y_0(12)|L(0)=\ell]} \leq \frac{\mathbb{E}[Y_{a(0),1,1}(V+12)|Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]}{\mathbb{E}[Y_{a(0),1,0}(V+12)|Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]} \text{ for a.s.-}\nu. \quad (4)$$

We will see that, if the above holds, then a lower bound on the efficacy of the ring versus placebo in the HOPE study will be available when $a(0)=1$.

We also suppose that (explain why...)

$$Y_{a(0),1,a(V)}(V+12) \perp\!\!\!\perp H_{a(0)}(V)|Y_{a(0)}(V)=0, L_{a(0),1}(V). \quad (5)$$

[4] The probability measure that should be plugged into the "♣" will be apparent once we give our identifiability result.

[5] we should check this with a subject-matter expert and see if they actually think the above is more plausible than the variant of the above that conditions on $H_{a(0)}(V)=1$ on the right

[6] As this individual-level efficacy involves the counterfactual outcomes under both the active and placebo interventions, it is not identifiable from the observed data. Consequently, this conjecture cannot be experimentally verified without untestable assumptions.

### 3.3 Identifiability result

By the law of total expectation,

$$\begin{aligned}
&\mathbb{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1] \\
&= \mathbb{E}\left[\mathbb{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)] \;\middle|\; H_{a(0)}(V)=1\right] \\
&= \int \mathbb{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]\, d\nu(\ell). \qquad (6)
\end{aligned}$$

Fix $\ell$ in the support of $\nu$. We have that

$$\begin{aligned}
&\mathrm{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell] \\
&= \frac{\mathrm{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]}{\mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]} \mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]
\end{aligned}$$

As $H_{a(0)}(V)=1$ implies that $Y_{a(0)}(V)=0$, we can add $Y_{a(0)}(V)=0$ to the event being conditioned on in the expectations that appear in the ratio above. Hence, the display continues as

$$\begin{aligned}
&= \frac{\mathrm{E}[Y_{a(0),1,0}(V+12) \mid Y_{a(0)}(V)=0, H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]}{\mathrm{E}[Y_{a(0),1,1}(V+12) \mid Y_{a(0)}(V)=0, H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]} \\
&\quad \times \mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]
\end{aligned}$$

As (5) holds, the display continues as

$$= \frac{\mathrm{E}[Y_{a(0),1,0}(V+12) \mid Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]}{\mathrm{E}[Y_{a(0),1,1}(V+12) \mid Y_{a(0)}(V)=0, L_{a(0),1}(V)=\ell]} \mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell]$$

By (3), the display continues as

$$= \frac{\mathbb{E}[Y_1(12)|L(0)=\ell]}{\mathbb{E}[Y_0(12)|L(0)=\ell]} \mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell] \qquad (7)$$

By (2), the display continues as

$$= \frac{\mathbb{E}[Y_1(12)|A(0)=1, L(0)=\ell]}{\mathbb{E}[Y_0(12)|A(0)=0, L(0)=\ell]} \mathrm{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1, L_{a(0),1}(V)=\ell, A(0)=a(0)]$$

By the consistency assumption, the display continues as

$$= \underbrace{\frac{\mathbb{E}[Y(12)|A(0)=1, L(0)=\ell]}{\mathbb{E}[Y(12)|A(0)=0, L(0)=\ell]}}_{\equiv f(\ell)} \underbrace{\mathrm{E}[Y(V+12) \mid H(V)=1, L(V)=\ell, A(0)=a(0)]}_{\equiv g(\ell)}.$$

This concludes our analysis of the inner expectation in (6). Plugging the above into (6) and then subsequently using (2) and the consistency assumption, we see that

$$\mathbb{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1] = \mathbb{E}\left[f(L_{a(0),1}(V))g(L_{a(0),1}(V)) \;\middle|\; H_{a(0)}(V)=1\right]$$

$$
\begin{aligned}
&= \mathbb{E}\left[f(L_{a(0),1}(V))g(L_{a(0),1}(V)) \;\middle|\; A(0)=a(0), H_{a(0)}(V)=1\right] \\
&= \mathbb{E}\left[f(L(V))g(L(V)) \mid A(0)=a(0), H(V)=1\right].
\end{aligned}
$$

The identifiability results for when $a(V)=1$ is more straightforward:

$$
\begin{aligned}
\mathbb{E}[Y_{a(0),1,1}(V+12) \mid H_{a(0)}(V)=1] &= \mathbb{E}\left[Y_{a(0),1,1}(V+12)\middle|\; A(0)=a(0), H_{a(0)}(V)=1\right] \\
&= \mathbb{E}\left[Y_{a(0),1,1}(V+12) \;\middle|\; A(0)=a(0), H(V)=1\right] \\
&= \mathbb{E}\left[Y(V+12) \mid A(0)=a(0), H(V)=1\right].
\end{aligned}
$$

### 3.4 Partial identifiability result

The same logic that was used above can be applied to obtain a lower bound for efficacy if instead of assuming (3), we assume (4). The only change that would occur is that the equality given in (4) would be replaced by $\geq$. This would result in the following partially identifiable result:

$$
\mathbb{E}[Y_{a(0),1,0}(V+12) \mid H_{a(0)}(V)=1] \geq \mathbb{E}\left[f(L(V))g(L(V)) \mid A(0)=a(0), H(V)=1\right].
$$

### 3.5 Estimation strategy

♣

## 4 Algorithms used for Superlearner

Every part of our identified parameter is a conditional expectation. While some of these conditional expectations can be estimated using empirical means, others will be more difficult due to the many variables conditioned on and the many possible values these variables can take. To estimate these conditional means so as to provide the most asymptotically efficient estimate of our parameter, we will use the superlearner.

This enseble learning methodology evaluates the performance of many different prediction algorithms based on cross validated accuracy. Then a convex combination of these algorithms is taken to create an optimal prediction function.

The random selection of the subsets used for cross validation will lead to small changes in the estimates and standard errors each time the algorithm is run. To minimize this randomness, the superlearner algorithm is run XXXX times to and the mean across these runs is taken to reduce the random variation in our estimate.

TO DO:

1. Derive IF
2. Describe how to use IPCW to deal with censoring (or do something more efficient)

Table 1: Super Learner Algorithms used

| | Description | R function |
|---|---|---|
| Classical Algorithms | Logistic Regression, Main Terms | `glm` |
| | Logistic Regression, Main and Interaction Terms | `glm` |
| | Logistic Regression, Main Terms, Forward Selection | `stepAIC` |
| Data Adaptive Algorithms | Random Forest | `ranger` |
| | Logistic regression Main terms with Lasso penalty | `glmnet` |
| | Logistic regression Main and Interaction Terms with Lasso penalty | `glmnet` |

3. ✓Add bound to previous section — the partial identifiability result that uses (4)
4. List covariates that we'd like to include (from protocols). I am not really sure what makes a variable we would like to include (without any underlying understanding of the relationship between all the variables, why not include them all?). At the very least, I think we should have data from the blood, urine, and pelvic samples and measures of adherence. It would also probably be useful to have data on which services they chose to receive:
   - Condoms
   - Used/unused study VR(s)
   - Provision of study VR(s)
   - Digital exam by clinician to check VR placement*
   - Protocol adherence
   - HIV/STI risk reduction
   - HIV pre- and post-test

   Many of these variables are longitudinal, but that should be fine as this can be handled by the ltmle package.
5. ✓Ask Elizabeth for data sets
6. ✓Add identifiability result for when $a(V) = 1$
7. ✓Specify how the SL will be made reproducible (see SAP for HIV project with Ernesto). Table with learners, how we'll ensure the output is stable, i.e. doesn't rely too much on choice of seed

# A Specifications of arguments to `ltmle` package

♣